1654
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Yuan-Tsong Chen		
Application No.:	09/902,461	Group:	1654
Filed:	July 10, 2001	Examiner:	M. Meller
Confirmation No.:	6796		
For:	TREATMENT OF GLYCOGEN STORAGE DISEASE TYPE II		

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, P.O. Box 2327, Arlington, VA 22202

on 3/10/03 Christina McSweeney
Date Signature

Christina McSweeney
Typed or printed name of person signing certificate

TRANSMITTAL OF DECLARATION
UNDER 37 C.F.R.§1.132 OF DR. YUAN-TSONG CHEN

Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Sir:

Please find enclosed herewith the original executed Declaration Under 37 C.F.R.§1.132 of Dr. Yuan-Tsong Chen for filing in the above-captioned application. A faxed copy was filed with the U.S. Patent and Trademark Office on March 3, 2003.

Please charge any deficiency or credit any overpayment in the fees that may be due in this matter to Deposit Account No. 08-0380. A copy of this letter is enclosed for accounting purposes.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

David C. Brook, RN 22592

By for Elizabeth W. Mata
Elizabeth W. Mata
Registration No.: 38,236
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133
Date: 3/10/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Yuan-Tsong Chen		
Application No.:	09/902,461	Group:	1651
Filed:	July 10, 2001	Examiner:	M. Meller
Confirmation No.:	6796		

For: TREATMENT OF GLYCOGEN STORAGE DISEASE TYPE II

CERTIFICATE OF MAILING
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on 3/16/03 Christina M Sweeney
Date Signature
Christina M Sweeney
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DECLARATION UNDER 37 C.F.R. §1.132

OF DR. YUAN-TSONG CHEN

Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Sir:

I, Yuan-Tsong Chen, of 1066 Canterbury Lane, Chapel Hill, North Carolina, 27517, USA, hereby declare and state that:

1. I am the sole named inventor on the referenced patent application. I have reviewed this application prior to signing this Declaration.

2. I understand that the Examiner has rejected the claims of the application as being anticipated by, or obvious over, the Fuller *et al.* reference (Fuller *et al., Eur. J. Biochem. 234*:903-909 (1995)), and as being obvious over the Bijvoet *et al.* reference (Bijvoet *et*

al., Hum. Mol. Genet. 7(11):1815-1824 (1998)) in combination with the Fuller *et al.* reference.

3. Fuller *et al.* describe uptake of recombinant GAA in two types of cells from a patient having Glycogen Storage Disease Type II (GSD-II, "Pome's disease"): in cultured human skin fibroblasts after exposure to the enzyme for 12 hours, as well as in cultured human muscle cells after exposure to the enzyme for 24 hours. They indicate that lysosomal glycogen in the muscle cells was cleared, following addition of recombinant GAA to the culture medium of the cells.

4. Fuller *et al.* do not teach treatment of disease. Neither uptake of enzyme by cultured human fibroblasts, nor uptake of enzyme by cultured human muscle cells and subsequent processing of lysosomal glycogen in the muscle cells, both occurring in culture and in the short term (e.g., 12 to 24 hours) as described by Fuller *et al.*, indicates whether periodic administration of the GAA to a human patient having GSD-II will treat the disease, that is, by ameliorating one or more symptoms associated with the disease, preventing or delaying the onset of one or more symptoms of the disease, and/or lessening the severity or frequency of one or more symptoms of the disease. Furthermore, because Fuller *et al.* do not describe administration of enzyme to heart cells, they cannot teach treatment of cardiomyopathy. Cardiomyopathy is the primary cause of death in pediatric patients having GSD-II.

5. Furthermore, one would not have known whether GAA administered to a whole individual (in contrast with administration to cells in a culture) would have been able to treat the disease. One of ordinary skill in the art would not have known whether treatment would be successful, especially because there was no previously known treatment available for any genetic disease affecting heart and muscle. The teachings of Fuller *et al.* do not provide a reasonable expectation that administration of the enzyme to a patient periodically, for more than one dose, will, in fact, treat the disease. One would not have known whether administration of GAA to a whole individual would result in uptake of

the enzyme in the desired tissues (e.g., heart, skeletal muscle), or to the relevant part of the tissues (the myocytes), for treatment to be efficacious. Thus, given the Fuller *et al.* reference, one would not have known, whether it would be possible to treat disease, such as by ameliorating one or more symptoms associated with the disease, preventing or delaying the onset of one or more symptoms of the disease, and/or lessening the severity or frequency of one or more symptoms of the disease).

6. Bijvoet *et al.* describe production of transgenic recombinant hGAA in mouse milk; administration of a single dose of GAA to GSD-II knockout mice, and a resultant increase of enzyme activity in heart and skeletal muscle samples after two days; and the uptake of the enzyme by cultured human fibroblasts. Bijvoet *et al.* do not describe administration of GAA to a human individual, nor do they describe administration of GAA periodically, at an administration interval. Instead, Bijvoet *et al.* describe use of a single dose of enzyme. Bijvoet *et al.* describe increased activity in homogenized mouse heart and muscle tissue; however, these experiments do not indicate whether the enzyme has located to the relevant cells (e.g., myocytes), that will allow it to treat disease (e.g., by decreasing glycogen and/or decreasing symptoms). Normally, one would expect that intravenous administration of enzyme would result in the presence of the enzyme in the blood stream and endothelium of blood vessels, rather than in target cells elsewhere in the body.

7. Neither uptake of enzyme by cultured human fibroblasts, nor administration of a single dose of GAA to GSD-II knockout mice and resultant increase of enzyme activity, as described by Bijvoet *et al.*, or by the combination of Bijvoet *et al.* and Fuller *et al.*, indicates whether periodic administration of the GAA to a human patient having GSD-II will treat the disease, that is, by ameliorating one or more symptoms associated with the disease, preventing or delaying the onset of one or more symptoms of the disease, and/or lessening the severity or frequency of one or more symptoms of the disease. Increase of enzyme activity in knockout mice administered a single dose of the enzyme, does not indicate whether administration of the GAA periodically at an administration interval to a

patient will, for example, ameliorate one or more symptoms associated with the disease, prevent or delay of the onset of one or more symptoms of the disease, and/or lessen of the severity or frequency of one or more symptoms of the disease. Bijvoet *et al.* do not demonstrate the that the increase in activity is in the myocyte or skeletal muscle cells; rather, they demonstrate only that it is present in homogenized samples of the selected tissues; therefore, no indication of appropriate targeting of the enzyme is indicated, since the enzyme may merely be in the endothelial cells. Even if the enzyme located to the desired cells, Bijvoet *et al.* do not demonstrate a decrease of glycogen or other correction of symptoms. Without a demonstration of correction or amelioration of symptoms, one of ordinary skill in the art would have had no way to predict whether the methods would be effective to treat human individuals.

8. In contrast, as described in detail in the Example in the application, periodic administration of GAA produced in Chinese hamster ovary cells, to three separate patients, resulted in significant amelioration of symptoms associated with the disease, as well as delay in onset of more severe symptoms. For example, significant improvements in cardiac parameters were noted; pulmonary function and skeletal muscle functions improved and remained normal in one patient; neurologic and developmental characteristics were improved or remained normal. The successful reversal of certain symptoms in all patients, as well as the normal muscle functions, neurologic and developmental characteristics of the third patient, were highly significant because it was previously unknown whether human symptoms could be alleviated or whether normal development could be achieved by administration of GAA. Without treatment, these children would have died; more than 90% of all GSD-II patients die before one year of age. This is the very first example of successful treatment of an otherwise fatal genetic disease affecting heart and muscle.

I further declare that all the statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful false statements and the like made by me are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Yuan-Tsong Chen

Yuan-Tsong Chen

Date: March 3, 2003